(19) Europäisches Patentamt
European Patent Offic
Office européen d s brev ts

(11) Publication number: **0 008 203**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 79301564.5

(22) Date of filing: 03.08.79

(51) Int. Cl.³: C 07 D 277/34, C 07 D 417/12, A 61 K 31/425, A 61 K 31/44 // C07C93/06, C07D277/64

(30) Priority: 04.08.78 JP 95673/78

(43) Date of publication of application: 20.02.80 Bulletin 80/4

(84) Designated Contracting States: BE CH DE FR GB IT NL

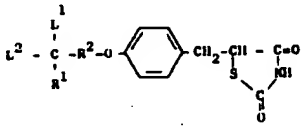
(71) Applicant: Takeda Yakuhin Kogyo Kabushiki Kaisha, 27, Doshomachi 2-Chome, Higashi-ku Osaka, (541) (JP)

(72) Inventor: Yutaka, Kauramatsu, 15-3, Oharano-Kamisatotorimicho, Nishikyo-ku, Kyoto 610-11 (JP)
Inventor: Takesku, Fujita, 13-15, Nagaodai 1-chome, Takarazuka, Hyogo 665 (JP)

(74) Representative: Lewin, John Harvey et al, Elkington and Fife High Holborn House 52/54 High Holborn, London WC1V 6SH (GB)

(54) Thiazolidine derivatives, preparing same and pharmaceutical compositions comprising same.

(57) Thiazolidine derivations of the general formula:



wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group including one or two hetero-atoms selected from nitrogen, oxygen and sulphur or a group of the formula

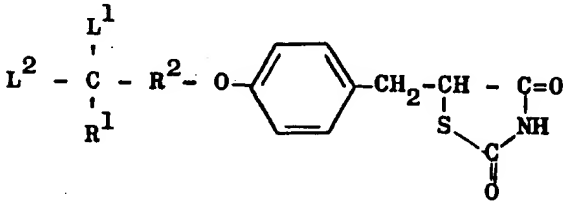
(where R^3 and R^4 are the same or different and each is lower alkyl or R^3 and R^4 are combined with each other either directly or interrupted by a hetero-atom selected from nitrogen, oxygen and sulphur to form a five- or six-membered ring); R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each is lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that, when R^1 is other than alkyl, L^1 and L^2 may be further hydrogen,
are novel compounds and useful as, for example remedies for diabetes, hyperlipemia and so on of the mammals including human beings.

EP 0 008 203 A1

Title

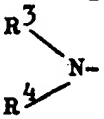
Thiazolidine Derivatives, Preparing Same and Pharmaceutical Compositions Comprising Same

This invention relates to novel thiazolidine derivatives having hypolipidemic and hypoglycemic activities with low toxicity. More particularly, the invention provides thiazolidine derivatives of the general formula (I) and salts thereof:



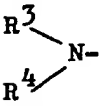
(I)

wherein R^1 is alkyl, cycloalkyl, phenyalkyl, phenyl, a five- or six-membered heterocyclic group including one or two hetero-atoms selected from nitrogen, oxygen and sulphur, or a group of the formula

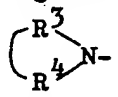


(where R^3 and R^4 are the same or different and each means lower alkyl or R^3 and R^4 are combined with each other either directly or interrupted by a hetero-atom selected from nitrogen, oxygen and sulphur to complete a five- or six-membered ring together with the nitrogen atom adjacent to R^3 and R^4); R^2 is a bond or a lower alkylene group; L^1 and L^2 may be the same or different and each is lower alkyl or L^1 and L^2 are combined with each other to form an alkylene group, provided that, when R^1 is ther than alkyl, L^1 and L^2 may further be hydrogen.

Referring to the general formula (I), the alkyl group R^1 may be a straight-chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; the cycloalkyl group R^1 may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R^1 may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. Examples of the heterocyclic group R^1 include 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from nitrogen, oxygen and sulphur, such as pyridyl, thienyl, furyl or thiazolyl. When R^1 is

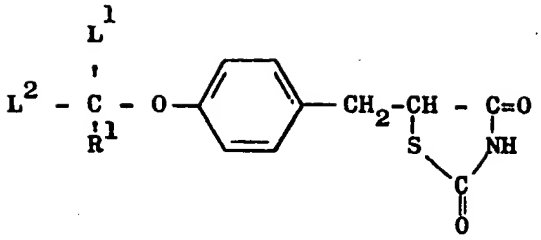


, the lower alkyls R^3 and R^4 may each be a lower alkyl of 1 to 4 carbon atoms such as methyl, ethyl, n-propyl, i-propyl and n-butyl. When R^3 and R^4 are combined with each other to complete a 5- or 6-membered heterocyclic group together with the adjacent N atoms, i.e. in the form of



, this heterocyclic group may include a further hetero-atom selected from nitrogen, oxygen and sulphur, as exemplified by piperidino morpholino, pyrrolidino and piperazino.

The lower alkylene group R^2 may contain 1 to 3 carbon atoms and, thus, may for example be methylene, ethylene or trimethylene. The bond R^2 is equivalent to the symbol "-", "." or the like which is used in chemical structural formulae, and when R^2 represents such a bond, the compound of general formula (I) is represented by the following general formula (II):

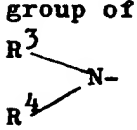


(II)

Thus, when R^2 is a bond, the atoms adjacent thereto on both sides are directly combined together.

Examples of the lower alkyls L^1 and L^2 include lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed when L^1 and L^2 are joined together is a group of the formula $-(CH_2)_{\underline{n}}-$ [where $\underline{n}$ is an integer of 2 to 6].

The cycloalkyl, phenylalkyl, phenyl and heterocyclic groups mentioned above, including the heterocyclic group  , may have 1 to 3 substituents in optional positions on the respective rings. Examples of such substituents include lower alkyls (e.g. methyl or ethyl),lower alkoxy groups (e.g. methoxy or ethoxy), halogens (e.g. chlorine or bromine) and hydroxyl. Also within the scope of the general formula (I) is an alkylenedioxy group of the formula $-O-(CH_2)_{\underline{m}}-O-$ [$\underline{m}$ is an integer of 1 to 3], such as methylenedioxy, which is attached to two adjacent carbon atoms on the ring to form an additional ring.

The compound (I) according to this invention can be converted to various salts by procedures known per se. For example, when the heterocyclic group R^1 includes a tertiary nitrogen atom, or R^1 means a group of the formula 

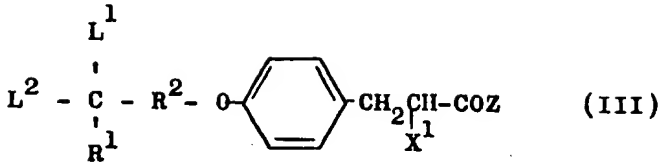
the compound (I) can be converted to acid salts with

acids, such as hydrochloric acid, sulphuric acid , acetic acid or oxalic acid. When R^1 does not include a tertiary nitrogen atom, the compoundmay be converted to salts with cations such as sodium ion, potassium ion, calcium ion or ammonium ion.

The thiazolidine derivative (I) according to this invention has activity to lower the blood sugar and triglyceride levels in mice (KKAy) with spontaneous diabetes and is expected to be of value in the treatment of hyperlipemia , diabetes and their complications in mammals including human beings. The compound (I) has low toxicity. For example, the LD_{50} value of 5-[4-(1-methylcyolohexylmethyloxy)benzyl] thiazolidine-2,4-dione in the rat is more than 10 g/kg. (P.O.). The compound (I) may be orally adminstered in dosage forms such as tablets, capsules, powders or granules, or by other routes in such forms as injections, suppositories, pellets and so on. The compound (I) may be mixed with a non-toxic, pharmaceutically acceptable carrier or diluent. Taking the treatment of hyperlipemia as an example, the compound may be orally or otherwise adminstered at a normal daily dose level of 50 mg to 1 gram per adult human. For treatment of diabetes, the compound [I] may be orally or otherwise adminstered at a normal daily dose of 10 mg to 1 gram per adult human.

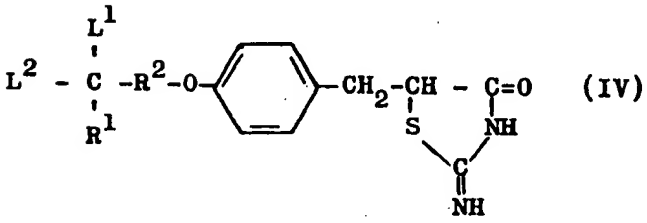
The thiazolidine derivative (I) of this invention may be produced, for example, by the following methods.

(1) The thiazolidine derivative (I) can be produced by the steps of reacting a compound of the general formula (III) with thiourea to obtain an 2-iminothiazolidine derivative of the general formula (IV) and, then, hydrolyzing the last-mentioned derivative (IV).



(III)

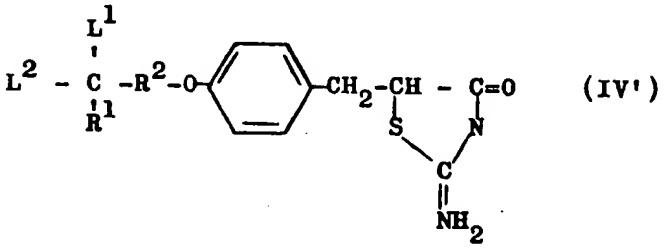
wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore; X^1 means halogen (e.g. chlorine or bromine), alkylsulphonyloxy (e.g. methylsulphonyloxy) or arylsuphonyloxy (e.g. toluenesulphonyloxy); Z is lower alkoxy (e.g. methoxy or ethoxy), hydroxyl, amino or a group of the formula -OM (M is, for example, an alkali metal atom, e.g. Na or K, or NH_4).



(IV)

wherein R^1, R^2, L^1, and L^2 have the meanings respectively defined hereinbefore.

The compound (IV) may tautomerically take the form as below:



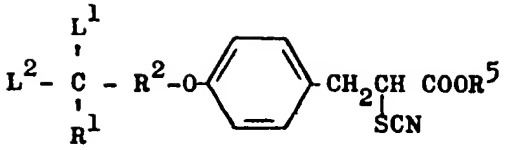
(IV')

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore]. The compound (IV') is also included within the scope of this inv nti n. In this

specification, the nomenclature and formula of these compounds are described en bloc as "2-iminothiazolidine derivative" and as formula (IV), repespectively.

The reaction between a compound (III) and thiourea is normally conducted in a solvent. Examples of such solvents include alcohols (e.g. methanol, ethanol, propanol, butanol or ethylene glycol monomethyl ether), ethers (e.g. tetrahydrofuran or dioxane), acetone dimethylsulphoxide, sulpholane, and dimethylformamide. While the relative amounts of starting materials need not be critically controlled, it is normally desirable to employ a slight excess of thiourea based on compound (III). Thus, 1 to 2 molecular equivalents of thiourea are preferably employed relative to compound (III). While the conditions of reaction such as reaction temperature and time depend on such factors as the starting material, solvent, etc., this reaction is normally carried out at the boiling point of the solvent used or at 100 to 130°C for a few to ten and odd hours. The sparingly soluble imino-compound (IV) is produced in the above manner. This imino-compound (IV) may be isolated prior to the following hydrolysis step or the reaction mixture containing (IV) may be directly hydrolyzed. In the hydrolysis step, the imino-compound (IV) is heated in a suitable solvent (e.g. sulpholane) and in the presence of water and mineral acid. The acid just mentioned is added normally in a proportion of 0.1 to 10 molecular equivalents, preferably 0.2 to 3 equivalents, based on compound (III), while water is used normally in a large excess based on compound (III). The heating time normally ranges from a few hours to 10 and odd hours.

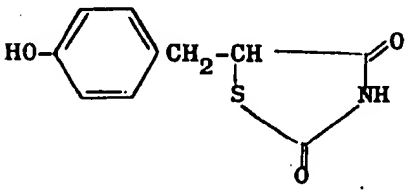
(2) The thiazolidin derivativ (I) can further b produced by subjecting a compound of the formula (V):



(V)

wherein L^1, L^2, R^1 and R^2 have the meanings given above, and R^5 means alkyl having 1 to 4 carbon atoms (e.g. methyl, ethyl, n-propyl, n-butyl or t-butyl), aryl having 6 to 8 carbon atoms (e.g. tolyl) or aralkyl having 7 or 8 carbon atoms (e.g. benzyl)to a cyclization reaction. This cyclization reaction is usually carried out by hydrolyizing a compound (V) with water. The hydrolysis is generally conducted in the presence of a catalyst, examples which include hydrogen halides (e.g. hydrogen chloride or hydrogen bromine), or mineral acids such as hydrochloric acid or sulphuric acid. The catalyst may generally be used in amount of from 20 to 50 mol equivalent relative to the compound (V). This reaction may be conducted in the presence of an organic solvent such as an alcohol (e.g. methanol or ethanol). While the reaction temperature varies with the type of catalyst used, the reaction may generally be carried out at a temperature ranging from 50 to 150°C. The reaction time is usually in the range of from 2 to 30 hours.

(3) The thiazolidine derivative (I)can also be produced by reacting a compound of the formula (VI):



(VI)

with a compound of the formula (VII):

$$L^2 - \underset{R^1}{\overset{L^1}{C}} - R^2 - X^2 \qquad \text{(VII)}$$

wherein L^1, L^2, R^1 and R^2 have the meanings given above, and X^2 means a halogen atom such as chlorine or bromine, in the presence of a base. Examples of the base, include sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide and sodium hydroxide. This reaction is usually carried out in the presence of a solvent. Suitable solvents include dimethylformamide and dimethylsulphoxide. The reaction temperature may be in the range of from room temperature to 100°C.

The resulting thiazolidine derivative (I) can be isolated and purified by conventional procedures such as concentration at atmospheric or subatmospheric pressure, solvent extraction, crystallization, recrystallization, phasic transfer or chromatography.

The compound (III) which is used as the starting material in the above preparation method (1) can be produced, for example, by the steps of diazotizing the corresponding aniline compound and subjecting the diazo-compound to Meerwein arylation.

The following reference and working Examples are given to illustrate this invention in further detail.

Reference Example 1

19.0 g of 4-[2-(N,N-dibutylamine)ethyloxy] nitrobenzene are dissolved in 200 ml of methanol and, after 3 g of 10% Pd-C (50% wet) are added, catalytic reduction is carried out at atmospheric temperature and pressure. The reaction system absorbs about 4,4ℓ of hydrogen in 75 minutes. The catalyst is then filtered off, th filtrate is concentrated under reduced pressure and the oily residue is dissolved in a mixtur of 100 ml

methanol and 100 ml acetone. Following the addition of 21.5 ml of concentrated hydrochloric acid, the solution is cooled to 0°C and a solution of 4.9 g sodium nitrite in 10 ml water is added dropwise at a temperature not exceeding 5°C. The mixture is stirred at 5°C for 20 minutes, at the end of which time 33.3g (34.9 ml) of methyl acrylate are added. The reaction mixture is heated to 35°C and 1 g or cuprous oxide is added in small portions, whereupon the temperature of the reaction system rises to 44°C with the evolution of nitrogen gas. The mixture is stirred for one hour and after the temperature has dropped to room temperature, it is allowed to stand overnight. The solvent is then distilled off under reduced pressure and the residue is made strongly basic with concentrated aqueous ammonia. Then, following the addition of water, extraction is carried out with ethyl acetate. The extract is washed with water, dried over sodium sulphate and distilled to remove the ethyl acetate. The oily residue is chromatographed on a column of 200 g silica gel, elution being carried out with ether-n-hexane (1:4). The above procedure yields 10.7 g (44.8%) of methyl 2-chloro-3-{4-[2-(N,N-dibutylamino)ethyloxy]phenyl} propionate.

IR(liquid film) $\nu_{max}^{cm^{-1}}$: 2945, 2850, 1745,1605, 1505
1250, 1170, 1030

NMR δ ppm $CDCl_3$: 0.93(6H,t), 1.2-1(8H,m), 2.52(4H,t), 2.83(2H,t), 3.0-3.5(2H,m), 3.7(3H,s). 4.0(2H,t), 4.4(1H,t), 6.75-7.30(4H,q)

Example 1

a) A mixture of 3.6 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate, 0.73 g of thiourea and 3 ml of sulpholane is heated at 120°C for 4 hours and, after cooling, 15 ml f water are added. The il is separated, ether is added to the oil and the crystalline

insolubles (a) are separated from the solution (b) by filtration. The filtrate (b) is distilled to remove the solvent and the residue is run onto a column of 100 g of silica gel, elution being carried out with chloroform. The above procedure yields 1.7 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione. m.p. 107-108°C (benzene-ligroin)

On the other hand, the crystals (a) are recrystallized from ethanol-acetone (3:1) to obtain 1 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)benzyl] thiazolidine-4-one with a decomposition point of 210-212°C. A 300 mg portion of this crystalline product is boiled with 2 ml of sulpholane and 2ml of 6N-HCl at 110°C for 5 hours. After cooling, 50 ml of water are added and the resulting crystals are recrystallized from benzene-ligroin. The above procedure yields 250 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl] thiazolidine-2,4-dione.

Example 2

A mixture of 27 g of ethyl 2-chloro-3-[4-(2-phenylpropyloxy)phenyl]propionate, 11 g of thiourea and 60 ml of sulpholane is heated at 110°C for 6 hours and, then, boiled with 10 ml of 2N-sulphuric acid (or 2 ml of 6N-HCl) for 16 hours. After cooling, 1 ℓ of water is added and the oil is separated and allowed to stand for a while, whereupon crystals separate out. These crystals are recrystallized from benzene-ligroin. The above procedure yields 19.9 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

Example 3

a) 333mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy) phenyl]propionic acid and 150 mg of thiourea are heated with 2 ml of sulpholane at 120°C for 1.5 hours and, following the addition of 2 ml of 6N-HCl, the mixture is further heated for 5 hours, at the end of which time 10 ml of wat r are added. The r sulting crystals are recovered by filtration. The above procedur yields 310

mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl] thiazolidine-2,4-dione.

b) The same procedure as that described in a) is repeated except that 355 mg of sodium 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate are employed. This procedure yields 310 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

c) The same procedure as that described in a) is repeated except that 332 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionamide are employed. This procedure yields 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]thiazolidine-2,4-dione.

d) 1.8 g of ammonium 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate and 0.8 g of thiourea are dissolved in 10 ml of ethanol and the solution is heated for 5 hours, at the end of which time 50 ml of water are added.

The above procedure yields 1.6g of 2-imino -5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidin-4-one.

Example 4

200 mg of 2-bromo-3-[4-(4-chlorobenzyloxy)phenyl] propionic acid and 100 mg of thiourea are dissolved in 2 ml of dimethylsulphoxide and the solution is heated at 110°C for 3 hours. Then, after 0.5 ml of water is added, the solution is further heated for 5 hours. Then, 10 ml of water are added and the resulting crystals are recovered by filtration and recrystallized from benzene-n-hexane (1:1). The above procedure yields 170 mg of 5-[4-(4-chloro-benzyloxy)benzyl]thiazolidine-2,4-dione.

Example 5

1.9 g of ethyl 3-[4-(2-methyl-2-phenylpropy-loxy)phenyl]-2-thiocyanatopropionate is dissolved in 20 ml of ethanol and 20 ml of 6N-hydr chloric acid are

added to the solution. The mixture is refluxed for 24 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ether. The extract is washed with water and then dried. After distilling off ether, the residue is crystallized from ether-n-hexane, whereby 730 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione are obtained.

Example 6

2.1 g of ethyl 2-methanesulphonyloxy-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate and 0.76 g of thiourea are added to 20 ml of sulpholane, and the mixture is heated at 120°C with stirring for one hour. After adding 10 ml of 2N-hydrochloric acid, the mixture is heated at 100°C for 8 hours. After cooling, water is added to the mixture, and the mixture is subjected to extraction with ether. The extract is weshed with water and dried. The ether is distilled off to give 1.3 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

Example 7

2.0 g of ethyl 2-methanesulphonyloxy-3-[4-(1-methylcyclohexylmethyloxy)phenyl]propionate and 760 mg. of thiourea are added to 20 ml of ethanol. The mixture is refluxed for 2 hours. 10 ml of hyrochloric acid, are added to the mixture and the mixture is further refluxed for 16 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ethyl acetate. The extract is washed with water and dried. The ethyl acetate is distilled off to give 1.4 g of 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione. Crystallization from 85% ethanol give crystals melting at 130 to 131°C.

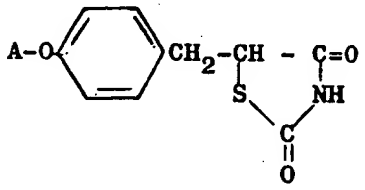
Example 8

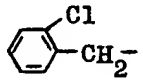
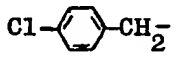
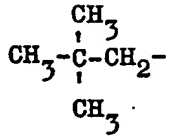
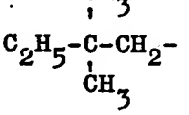
1.12 g of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione, is dissolved in 12 ml of dim thylsulphoxide and 480 mg of 50% sodium hydrid in oil are added to the solution.

The mixture is stirred at room temperature for 15 minutes, followed by addition of 0.81 g of 4-chlorobenzyl chloride. The whole mixture is stirred at 50°C for 4 hours. Water is added to the mixture and the mixture is acidified with 2N-hydrochloric acid. The mixture is subjected to extraction with ether. The extract is washed with water and dried. Ether is distilled off to give an oily substance. The oily substance is subjected to column chromatography on 30 g silica gel, elution being carried out with cyclohexane-ethyl acetate (2:1). The above procedure yields 425 mg of 5-[4-(4-chlorobenzyloxy)-benzyl]thiazolidine-2,4-dione.

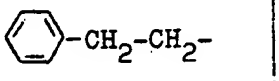
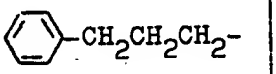
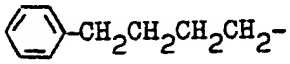
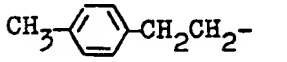
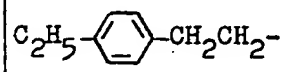
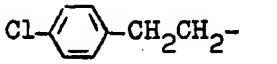
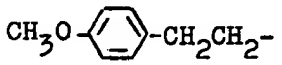
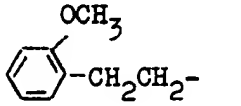
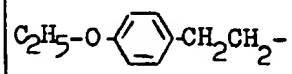
Example 9

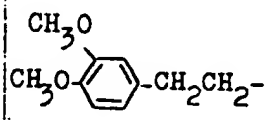
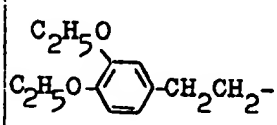
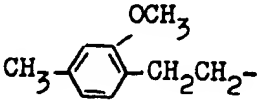
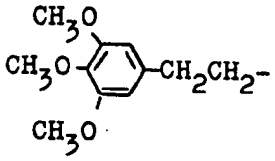
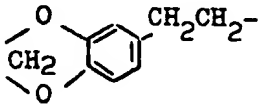
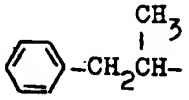
By procedures analogous to those described above in Examples 1 to 4, the following compounds were synthesized.

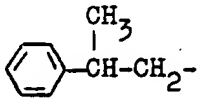
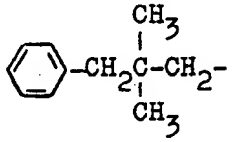
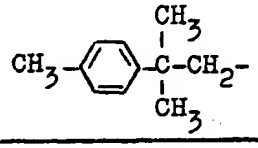
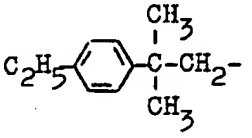
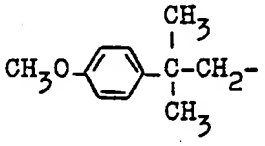
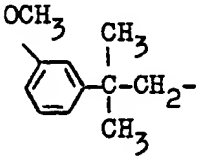
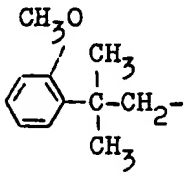


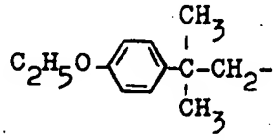
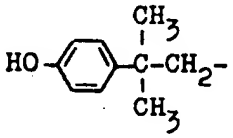
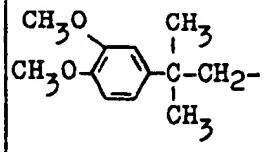
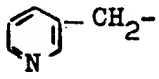
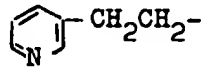
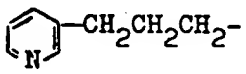
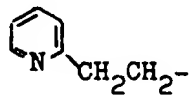
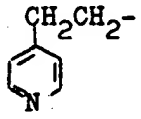
Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
1		benzene-n-hexane	85-86	1,4
2		benzene-cyclohexane	135-136	1
3		benzene-ligroin	156-158	1,3
4		Isopropyl ether	128-129	1

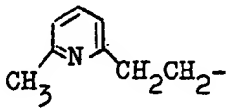
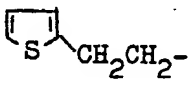
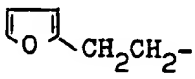
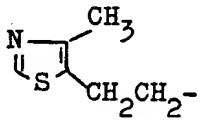
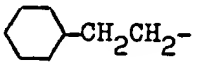
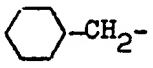
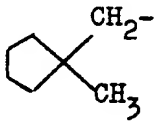
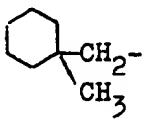
Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
5	$n\text{-}C_3H_7\text{-}C(CH_3)_2\text{-}CH_2\text{-}$	Ether-n-hexane	103-104	1,2
6	$n\text{-}C_4H_9\text{-}C(CH_3)_2\text{-}CH_2\text{-}$	Cyclohexane	102-103	1
7	$n\text{-}C_5H_{11}\text{-}C(CH_3)_2\text{-}CH_2\text{-}$	Cyclohexane	101-102	2
8	$n\text{-}C_6H_{13}\text{-}C(CH_3)_2\text{-}CH_2\text{-}$	Cyclohexane	101-102	2
9	$n\text{-}C_7H_{15}\text{-}C(CH_3)_2\text{-}CH_2\text{-}$	Cyclohexane	101-102	2
10	$CH_3\text{-}C(CH_3)_2\text{-}CH_2CH_2\text{-}$	Ether-n-hexane	101-102	1,2
11	$n\text{-}C_3H_7\text{-}C(C_2H_5)_2\text{-}CH_2\text{-}$	n-Hexane	69-70	2

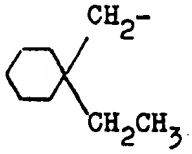
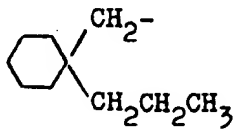
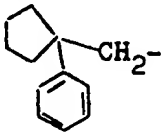
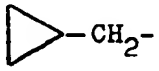
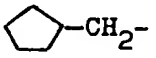
Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
12		Benzene-ligroin	93-94	1,3
13		Ethyl acetate-cyclohexane	79-80	1
14		Ethyl acetate-cyclohexane	82-83	1
15		Ethyl acetate-n-hexane	130-131	2
16		Ether-n-hexane	87-88	2
17		Ethyl acetate	148-149	2
18		Ethyl acetate-n-hexane	104-105	2
19		Ether-n-hexane	72-73	2
20		Ethyl acetate-n-hexane	102-103	2

Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
21		Ether-n-hexane	110-111	2
22			Oil IR(cm^{-1}) 3200, 1750, 1700, 1240 liquid film	2
23		Ethyl acetate-n-hexane	92-93	2
24		Ethyl acetate-n-hexane	108.5-109.5	2
25		Ethyl acetate-ether	132-133	2
26		Ether-n-hexane	84-85	1

Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
27		Ether-n-hexane	66-67	1,3
28		Ether-n-hexane	107-108	1
29		Cyclohexane	106-107	2
30		Ether-n-hexane	104-105	2
31		Ether-n-hexane	107-108	2
32		Ether-n-hexane	68-69	2
33		Ether-n-hexane	116-117	2

Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
34		Ether-n-hexane	87-88	2
35		Ether	157-158	2
36		Ether-n-hexane	106-107	2
37		Methanol	183-184	1
38		Chloroform-methanol	175-176	1,2
39		Chloroform-methanol	176-177	2
40		DMF-H_2O	209-210	1,2
41		Methanol	167-168	2

Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
42		Ethyl acetate-n-hexane	103-104	2
43		Ether-n-hexane	73-74	2
44		Ether-n-hexane	62-64	2
45		Ethanol	193-194.5	1
46		Cyclohexane	82-83	1
47		n-Propanol	121-122	1,2
48		Benzene-ligroin	137-138	1,2
49		Cyclohexane	124-125	1,5

Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s).
50		Ligroin	88-89	1
51		n-Hexane	68-69	1
52		Benzene-ligroin	136-137	1
53		Ether-n-hexane	88-89	2
54		Ether-n-hexane	110-111	2

Example 10

A mixture of 10.0 g methyl 2-chloro-3-[4-(2-morpholinoethyloxy)phenyl]propionate and 4.64 g thiourea is heated in the presence of 100 ml of sulpholane at 120°C for 4 hours. After cooling, a saturated aqueous solution of sodium hydrogen carbonate is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over sodium sulphate and distilled to remove the ethyl acetate, whereupon 4.1 g (40.2%) of 2-imino-5-[4-(2-morpholinoethyloxy)benzyl] thiazolidin-4-one are obtained as crystals. These crystals are recrystallized from ethyl acetate-methanol. Colourless needles, m.p.189-190°C.

4.1 g of the above 2-imino-5-[4-(2-morpholinoethyloxy)benzyl]thiazolidin-4-one are dissolved in 50 ml of 2N-HCl and the solution is heated under reflux for 16 hours. After cooling, the reaction mixture is neutralised with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over sodium sulphate and distilled to remove the ethyl acetate, whereupon 3.8 g (92.7%) of 5-[4-(2-morpholino-ethyloxy)benzyl]thiazolidine-2,4-dione are obtained as crystals. These crystals are recrystallized from dimethyl-formamide-water. Colourless prisms, m.p. 188-189°C.

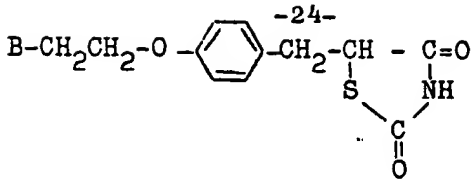
Example 11

A mixture of 9.0 g methyl 2-chloro-3-{4-[2-(N,N-diisopropylamino)ethyloxy]phenyl} propionate and 2.4.g thiourea is heated in the presence of 100 ml of n-butanol at 100°C for 15 hours. After cooling, the n-butanol is distilled off under reduced pressure, 100 ml of 2N-HCl are added to the residue and the mixture is heated at 100°C for 6 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried (over

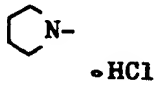
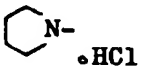
Na_2SO_4) and distilled to remove the ethyl acetate, whereupon 6.0 g (65.2%) of 5-{4-[2-(N,N-diisopropyl-amino)ethyloxy]benzyl} thiazolidine-2,4-dione are obtained as crystals. These crystals are recrystallized from ethanol. Colourless prisms, m.p. 134-135°C.

Example 12

By procedures analogous to those described in Examples 10 or 11, the following compounds were synthesized.



Compound No.	B	Recrystallization solvent	m.p.(°C)	Analogous Example No(s).
1	CH_3, CH_3, N- ·HCl	Ethanol	208-209	10,11
2	C_2H_5, C_2H_5, N- ·HCl	Ethanol	146-147	10,11
3	n-C_3H_7, n-C_3H_7, N-	Ethanol	124-125	11
4	i-C_3H_7, i-C_3H_7, N-	Ethanol	134-135	11
5	n-C_4H_9, n-C_4H_9, N-	Ethanol	98-99	10,11

Compound No.	B	Recrystallization solvent	m.p.(°C)	Analogous Example No(s).
6	 ·HCl	methanol	232-234	11
7	 ·HCl	methanol	244-245	11

Example 13

An example of a practical recipe in which the compound of this invention is utilized as a remedy for diabetes is as follows:

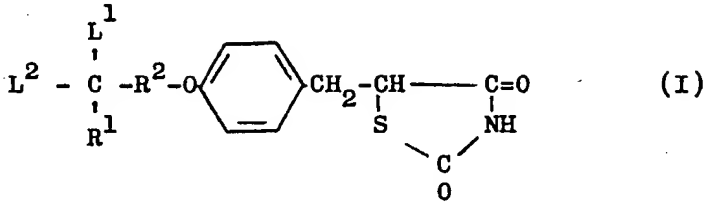
(Tablet)

(1)	5-[4-(1-methylcyclohexyl-methyloxy)benzyl] thiazolidine-2,4-dione	10. mg
(2)	lactose	35 mg
(3)	corn starch	170 mg
(4)	microcrystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
		250 mg per tablet

(1), (2), (3) and 2/3 quantity of (4) are thoroughly mixed, and then the mixture is granulated. The remaining 1/3 quantity of (4), and (5) are added to the granules and the product is compressed into tablets. The tablets thus prepared can further b coated with a suitable coating agent.

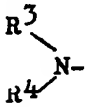
CLAIMS

1. A thiazolidine derivative of the general formula (I):



(I)

wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group including one or two hetero-atoms selected from nitrogen, oxygen and sulphur, or a group of the formula



(wherein R^3 and R^4 are the same or different and each is lower alkyl or R^3 and R^4 are combined with each other either directly or interrupted by a hetero-atom selected from nitrogen, oxygen and sulphur to form a five- or six-membered ring); R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each is lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that, when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen, or salts thereof.

2. A thiazolidine derivative as claimed in claim 1, wherein R^1 is an alkyl having 1 to 10 carbon atoms.

3. A thiazolidine derivative as claimed in claim 1, wherein L^1 and L^2 are combined to form an alkylene group having 2 to 6 carbon atoms.

4. A thiazolidine derivative as claimed in claim 1, wher in R^2 is a lower alkyl ne group having 1 to 3 carbon atoms.

5. A thiazolidine derivative as claimed in claim

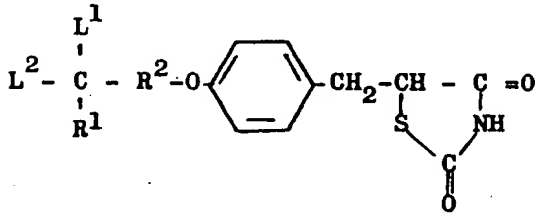
1, wherein R^1 is an alkyl having 1 to 10 carbon atoms; L^1 and L^2 are combined to form an alkylene group having 2 to 6 carbon atoms; and R^2 is a lower alkylene group having 1 to 3 carbon atoms.

6. A thiazolidine derivative as claimed in claim 1, which is 5-[4-(1-methylcylohexylmethyloxy) benzyl]thiazolidine-2,4-dione.

7. A pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative as defined in claim 1.

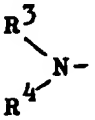
8. A pharmaceutical composition as claimed in claim 1, wherein the derivative is 5-[4-(1-methyl-cyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione.

9. A process for the production of a thiazolidine derivative of the general formula (I):



(I)

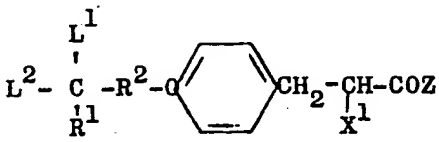
wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group including one or two hetero-atoms selected from nitrogen, oxygen and sulphur or a group of the formula



(where R^3 and R^4 are the same or different and each is lower alkyl or R^3 and R^4 are combined with each other either directly or interrupted by a hetero-atom selected from nitrogen, oxygen and sulphur to form a five- or six-membered ring); R^2 means a bond of a lower alkylene group;

L^1 and L^2 are the same or different and each is lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that, when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen,

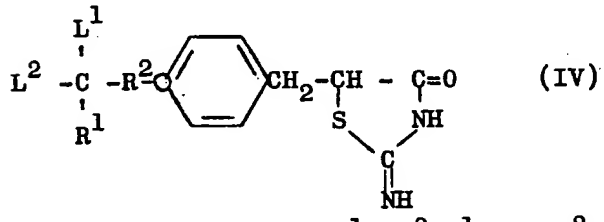
which process comprises reacting a compound of the formula (III):



(III)

wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined above; X^1 means halogen, alkylsulphonloxy or arylsulphonyloxy; and Z is lower alkoxy,

with thiourea to obtain an 2-iminothiazolidine derivative of the formula (IV):



(IV)

wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined above,

and, then hydrolyzing the last-mentioned 2-iminothiazolidine derivative.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 79 30 1564

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	CHEMICAL ABSTRACTS, vol. 83, no. 83, 8th December 1975, page 466, no. 193294u Columbus, Ohio, U.S.A. & SU - 480 711 (LENSOVET TECHNOLOGICAL INSTITUTE, LENINGRAD), 15-08-1975	1

CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)

C 07 D 277/34
417/12
A 61 K 31/425
31/44//
C 07 C 93/06
C 07 D 277/64

TECHNICAL FIELDS SEARCHED (Int.Cl. ³)

C 07 D 277/34
417/12
A 61 K 41/425

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hagu	31-10-1979	BRIGHENTI

EPO Form 1503.1 06.78